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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Kavanaugh et al.
Application No.	:	09/640,041
Filed	:	August 15, 2000
For	:	EGFH2 GENES AND GENE PRODUCTS

Examiner	:	Margaret E. Jamroz
Art Unit	:	1644
Docket No.	:	59516-135/PP-01615.002
Date	:	February 26, 2003

Commissioner for Patents
Washington, DC 20231

AFFIDAVIT OF DR. JUDITH ABRAHAM UNDER 37 C.F.R. § 1.132

Sir:

I, Judith Abraham, Ph.D., being duly sworn, say:

1. I am an internationally recognized scientist and am presently employed at Chiron Corporation, Emeryville, California (from June, 2000 to present), where I hold the position of Director, Research. I received a Bachelors degree in Biology from the University of California, Riverside, and a Ph.D. degree from the University of California, Berkeley, in Molecular Biology.

2. I am an author or co-author of more than 50 peer-reviewed research articles and have been invited to give numerous presentations on my research at national and international meetings. My curriculum vitae is attached.

3. In my capacity as Director of Research at Chiron Corporation, and in my prior work, I am familiar with identifying and characterizing proteins, based on homology (both sequence alignment and structural homology), using methods well-known to those or ordinary skill in the art at the time of filing of the above-identified patent application. I am also familiar

with methods of protein expression and methods of assaying biological activity of proteins, particularly growth factors.

4. I understand that claims of the above-referenced patent application are rejected under 35 U.S.C. § 112, first paragraph, on the grounds that although the specification is enabling for an isolated nucleic acid molecule comprising SEQ ID NO:3, which encodes a polypeptide comprising SEQ ID NO:4, the specification allegedly does not enable nucleic acids that encode polypeptides that are at least 90% identical to the polypeptide of SEQ ID NO:4.

5. I have reviewed the patent application referenced above entitled "EGFH2 Genes and Gene Products," and I am very familiar with the subject matter of the application. At page 7, lines 3-16, the application describes a family of receptors for neuregulins, referred to as ErbB. EGFH2 is also known as NRG4 (neuregulin 4) and functions by signaling through an ErbB receptor. Thus, the biological activity of the NRG4 of the invention can be assayed by measuring the effect of NRG4 binding to its ErbB receptor.

6. The receptor for NRG4 is known in the art as ErbB4, and is discussed in the patent application at page 7, lines 8-9. Binding of NRG4 to ErbB4 can be assayed using a known cell line that lacks endogenous ErbB4 expression (myeloid 32D cells) and which have been engineered to express ErbB4 receptors, as described in Pinkas-Kramarski *et al.*, *EMBO Jour.* 15:2452-2467 (1996) and Shelly *et al., J. Biol. Chem.* 273:10496-10505 (1998). Survival of these cells in the presence of NRG4 and in the absence of cytokine, such as IL-3, indicates functional binding of NRG4 (EGFH2) to the ErbB4 receptor.

7. Because this assay provides a definitive result, specifically the survival of a 32D cell line engineered to express ErbB4, one of skill in the art can use this system to assay proteins that have at least 90% sequence identity with EGFH2, as shown in SEQ ID NO:4. As a person of skill in the art, it is my opinion that it would entail only routine experimentation to express a nucleic acid encoding a polypeptide having at least 90% sequence identity with SEQ ID NO:4, and assay the polypeptide for its ability to bind ErbB4 and thereby permit the survival of 32D cells expressing ErbB4. These techniques were available in the art prior to the filing date of this

application, and are also conveniently summarized in Harari, D. *et al., Oncogene* 18:2681-2689, 1999, which, on information and belief, is of record in the application.

8. Paragraphs 5-7 above describe one assay for EGFH2 biological activity. A separate assay is disclosed in the application as filed at pages 38-39. Specifically, cDNA encoding EGFH2, or a polypeptide having at least 90% identity with SEQ ID NO:4, is cloned and transcribed, and the corresponding mRNA is obtained. The mRNA is injected, using routine methods, into *Xenopus* oocytes and the germinal vesicle breakdown is assayed. While antisense EGFH2 mRNA does not cause germinal vesicle breakdown, sense EGFH2 mRNA does, and the presence of germinal vesicle breakdown in oocytes injected with mRNA within the scope of the claims will indicate that the mRNA encodes functional EGFH2.

9. A third method for assaying the biological activity of a polypeptide having at least 90% identity to the EGFH2 of SEQ ID NO:4 entails expressing the polypeptide in a baculovirus – insect cell expression system, purifying the polypeptide using routine protein purification methods, and then assaying the ability of the polypeptide to stimulate phosphorylation of the receptor ErbB4. For this assay, the EGFH2 polypeptide is added to cells known to express ErbB4, such as the human breast cancer cell line MDA-MB-453 (Sepp-Lorenzino, L. *et al. Oncogene* 12:1679-1687, 1996). The ErbB4 from the cells can be readily isolated after cell lysis and membrane solubilization, by immunoprecipitation using an antibody specific for ErbB4. The precipitated protein is then fractionated by electrophoresis on a sodium dodecyl sulfate-polyacrylamide gel, and transferred to a membrane utilizing the technique of Western blotting. The degree of phosphorylation of the ErbB4 receptor is measured by probing the membrane with an antibody specific for phosphotyrosine. If the phosphotyrosine content of the ErbB4 receptor is higher in cells treated with the EGFH2 polypeptide than in control cells not exposed to the polypeptide, then the EGFH2 polypeptide is judged to be functional. The patent application as filed discloses ErbB4, and at the time of filing it was known that (a) antibodies to ErbB4 could be raised, and (b) ErbB4 is a tyrosine kinase and is capable of being phosphorylated, which can be detected using radiolabel or an anti-phosphotyrosine antibody, for example.

10. In conclusion, it is my opinion, as one of skill in this art, that the knowledge, techniques and reagents available at the time of filing of the above-identified patent application could be used to measure the EGFH2 biological activity of a polypeptide having at least 90% identity to SEQ ID NO:4.

11. I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Judith Abraham

State of California)
) ss.:
County of Alameda)

On this 25th day of February, 2003, before me, a Notary Public in and for the State and County aforesaid, personally appeared Judith Abraham, to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and she acknowledged the same to be her free act and deed.

Notary Public

NANCY L. SWANSON
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Commission expires 11/23/05

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Curriculum Vitae

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EDUCATION:

1971 - 1975 University of California, Riverside, California
B.A., Biology

1975 - 1980 University of California, Berkeley, California
Ph.D., Molecular Biology (Thesis Advisor: Harrison Echols)

EMPLOYMENT HISTORY:

1980 - 1983 **Cold Spring Harbor Laboratory**, Cold Spring Harbor, New York
Postdoctoral Fellow (Advisor: James Hicks)

1983 - 2000 **Scios Inc. / Scios Nova Inc. / California Biotechnology Inc.***

1983 - 1990 ***Staff Scientist***

1985 - 1989 FGF Project Leader (Research) / Manager (Development)
1989 - 1999 FGF Product Team Member (Clinical Testing Phase)
1988 - 1991 VEGF Project Leader

1990 - 2000 ***Principal Scientist***

1990 - 1993 HB-EGF Project Leader
1994 - 1996 Mac-1 Project Leader
1997 – 2000 VEGF Project Leader (Research) / Manager (Development)

2000 – present **Chiron Corporation**

2000 - 2001 ***Associate Director, Research***

2001 – present ***Director, Research***

** Scios Nova was formed through a merger of California Biotechnology and Nova Pharmaceutical Corp. in 1992; the name was subsequently shortened to Scios Inc.*

FELLOWSHIPS AND ACADEMIC HONORS:

1975	Phi Beta Kappa, University of California, Riverside Chapter
1975	Summa Cum Laude Graduate, University of California, Riverside
1975	Outstanding Student Award, College of Natural and Agricultural Sciences, University of California, Riverside
1975 - 1976	Regents Fellowship, University of California, Berkeley
1976 - 1980	Regents Intern Fellowship, University of California, Berkeley
1981 - 1983	Damon Runyon - Walter Winchell Postdoctoral Fellowship

MEMBERSHIPS AND SCIENTIFIC ORGANIZATION POSITIONS HELD:

American Society for Investigative Pathology

North American Vascular Biology Organization

The Wound Healing Society

Board of Directors, 1996 – 1999

Organizer, 1997 Annual Meeting

American Association for the Advancement of Science

American Heart Association

PUBLICATIONS:

1. **Abraham, J.A.**, D. Mascarenhas, R. Fischer, M. Benedik, A. Campbell, and H. Echols (1980) "DNA sequence of regulatory region for integration gene of bacteriophage lambda". *Proc. Natl. Acad. Sci. USA* **77**: 2477-2481.

2. **Abraham, J.A.**, and H. Echols (1981) "Regulation of int gene transcription by bacteriophage lambda: Location of the RNA start generated by an int constitutive mutation". *J. Mol. Biol.* **146**: 157-165.

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12. **Abraham, J.A.**, A. Mergia, J.L. Whang, A. Tumolo, J. Friedman, K.A. Hjerrild, D. Gospodarowicz, and J.C. Fiddes (1986) "Nucleotide sequence of a bovine clone encoding the angiogenic protein, basic fibroblast growth factor". *Science* **233**: 545-548.

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